A Potential New Treatment Paradigm for Multiple Sclerosis

Sameer Nikhar,[1] Alexei Degterev[2] and Gregory D. Cuny[1]

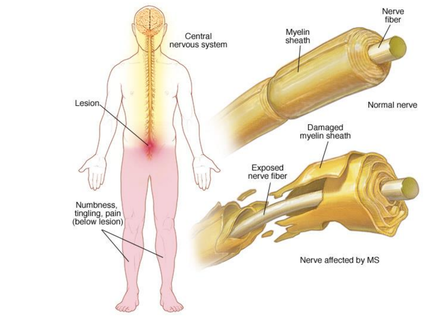
[1]Department of Pharmacological and Pharmaceutical Sciences, University of Houston, Houston, TX

[2]Department of Developmental, Molecular & Chemical Biology, School of Medicine, Tufts University, Boston, MA

Contact Information:
Sameer Nikhar
University of Houston
Phone: (619) 618-9945
Email: snikhar@uh.edu

Multiple Sclerosis (MS)

- Disease of Central Nervous System (Brain and Spinal Cord). 2 million affected globally.
- Autoimmune disease where immune system attacks protective myelin sheath surrounding nerve fibers.
- Neuro-inflammation causes communication problems in the brain and between the brain and peripheral tissues.



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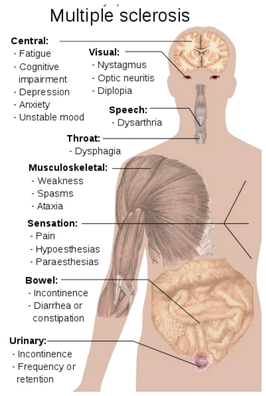


Wikipedia

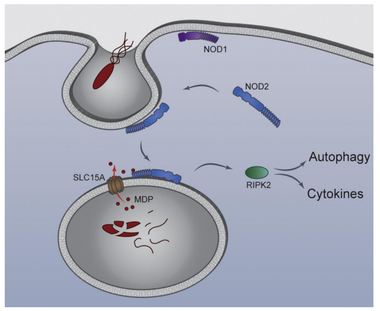
Causes: Genetic, environmental (e.g. bacterial & viral infections) and other factors (e.g. smoking).

Treatment: Immunosuppressants- Glucocorticoids, Monoclonal antibodies etc.

Immunomodulatory drugs that prevents lymphocytes from entering sites of inflammation.

Anti-inflammatory drugs that reduce pain.

RIPK2 as a Target for MS



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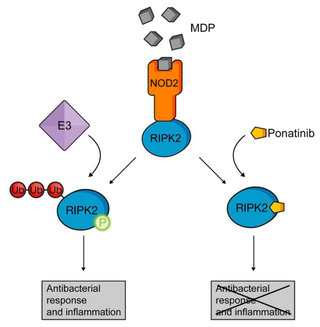

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- Immune cells (macrophages, dendritic cells) cross blood brain barrier (BBB).
- Bacterial fragments recognize by NOD1/2 proteins in immune cells.
- Receptor interacting protein kinase-2 (RIPK2) activated by NOD1/2 proteins.
- Resulting in synthesis of pro-inflammatory cytokines that cause neuro-inflammation.

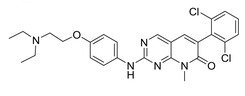
Finding Novel RIPK2 Inhibitors for Preventing Neuro-inflammation

Lead Identification

A

Type II inhibitors	Intermediate state DXG inhibitors
Imatinib	OSSL-648293
Ponatinib	F091-0488
Rebastinib	Vemurafenib
CS-0709	JNK inhibitor VIII
PF-431396	MLN8054
Doramaprimod	Alisertib (MLN8237)
Nilotinib	YL5-81-1
Bosutinib	PD166285/UH15
R406	
Dasatinib	
Tozasertib	
Sorafenib	
CS-R3	

B

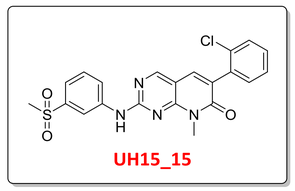


UH15

Compd Id	RIPK2 IC_{50} (nM)	ALK2 IC_{50} (nM)
UH15	10	9.3

Fig 1: A) Commercially available inhibitor screen and identification of PD166285/UH15 as lead compound. B) Structure of UH15 and its enzymatic activity against RIPK2 and ALK2

In Vitro DMPK Studies



UH15_15

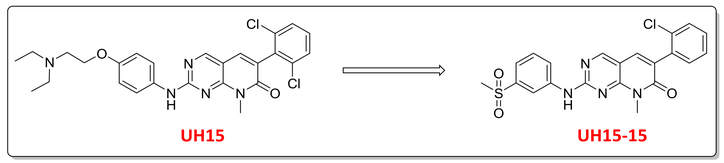
- LogP: 2.94
- Solubility: 0.7 µM (0.31 mg/mL)
- Permeability: 2.36 x 10^{-6} cm/sec
- Mouse liver microsome stability: Half-life ($t_{1/2}$): 20 min; Intrinsic Clearance (Cl_{int}): 35 µL/min/mg

Lead Optimization

A

Comp Id	RIPK2 IC_{50} (nM)	NOD2/RIPK2 IC_{50} (nM)	ALK2 IC_{50} (nM)
UH15	10	41	9
UH15_1	13	143	NI
UH15_2	12	4	61
UH15_8	13	707	2945
UH15_9	95	3000	NI
UH15_5	33	269	18
UH15_12	11	10	136
UH15_11	6	10	972
UH15_15	5	24	2516
UH15_23	377	TBD	TBD

B



UH15 → UH15-15

Fig 2: A) RIPK2 and ALK2 kinase and NOD2/RIPK2 cell signaling inhibitory activities for UH15 derivatives. B) Summary of UH15 optimization to generate UH15_15.

Conclusions & Future Directions

1) **PD166285/UH15** identified as lead compound. 2) **SAR** based optimization produced UH15_15. 3) **UH15_15** is a highly potent RIPK2 inhibitor. It also blocks NOD1/2-RIPK2 cell signaling. 4) It shows **modest** stability and permeability but low solubility. 5) Efforts towards **improving solubility** will be performed. 6) **Animal studies** in experimental autoimmune encephalomyelitis (EAE) mouse models will be performed.

References

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